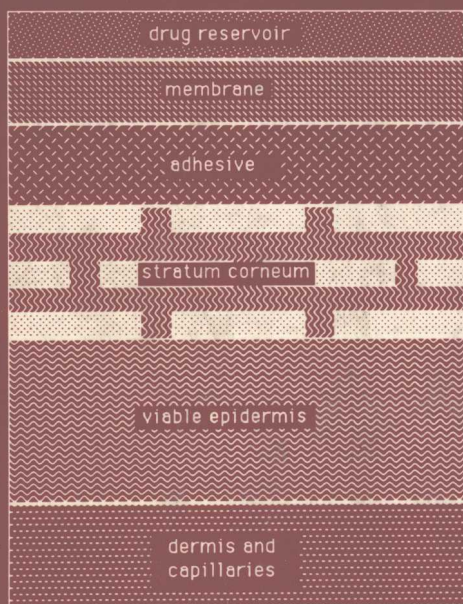


Transdermal Drug Delivery

Developmental Issues and Research Initiatives



edited by
Jonathan Hadgraft
Richard H. Guy

Transdermal Drug Delivery

Developmental Issues and Research Initiatives

edited by

Jonathan Hadgraft

*The Welsh School of Pharmacy
University of Wales Institute
of Science and Technology
Cardiff, Wales*



Richard H. Guy

*Departments of Pharmacy and Pharmaceutical Chemistry
University of California at San Francisco
San Francisco, California*



MARCEL DEKKER, INC.

New York and Basel

Library of Congress Cataloging-in-Publication Data

Transdermal drug delivery : developmental issues and research initiatives / edited by Jonathan Hadgraft, Richard H. Guy.

p. cm. -- (Drugs and the pharmaceutical sciences ; v. 35)

Includes bibliographies and index.

ISBN 0-8247-7991-6

1. Transdermal medication. 2. Skin--Physiology. I. Hadgraft, Jonathan. II. Guy, Richard H. III. Series.

[DNLM: 1. Administration, Cutaneous. 2. Administration, Topical.

3. Permeability. 4. Pharmacokinetics. 5. Skin--metabolism. W1

DR893B v. 35 / WB 340 T77234]

RM151.T75 1989

615'.66--dc19

DNLM/DLC

for Library of Congress

88-25778

CIP

Copyright ©1989 by MARCEL DEKKER, INC. All Rights Reserved

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

MARCEL DEKKER, INC.

270 Madison Avenue, New York, New York 10016

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Transdermal Drug Delivery

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

Edited by

James Swarbrick

School of Pharmacy

University of North Carolina

Chapel Hill, North Carolina

- Volume 1. PHARMACOKINETICS, *Milo Gibaldi and Donald Perrier*
(out of print)
- Volume 2. GOOD MANUFACTURING PRACTICES FOR
PHARMACEUTICALS: A PLAN FOR TOTAL QUALITY
CONTROL, *Sidney H. Willig, Murray M. Tuckerman, and*
William S. Hitchings IV (out of print)
- Volume 3. MICROENCAPSULATION, *edited by J. R. Nixon*
- Volume 4. DRUG METABOLISM: CHEMICAL AND BIOCHEMICAL
ASPECTS, *Bernard Testa and Peter Jenner*
- Volume 5. NEW DRUGS: DISCOVERY AND DEVELOPMENT,
edited by Alan A. Rubin
- Volume 6. SUSTAINED AND CONTROLLED RELEASE DRUG DELIVERY
SYSTEMS, *edited by Joseph R. Robinson*
- Volume 7. MODERN PHARMACEUTICS, *edited by Gilbert S.*
Banker and Christopher T. Rhodes
- Volume 8. PRESCRIPTION DRUGS IN SHORT SUPPLY: CASE
HISTORIES, *Michael A. Schwartz*
- Volume 9. ACTIVATED CHARCOAL: ANTIDOTAL AND OTHER
MEDICAL USES, *David O. Cooney*
- Volume 10. CONCEPTS IN DRUG METABOLISM (in two parts), *edited*
by Peter Jenner and Bernard Testa
- Volume 11. PHARMACEUTICAL ANALYSIS: MODERN METHODS
(in two parts), *edited by James W. Munson*
- Volume 12. TECHNIQUES OF SOLUBILIZATION OF DRUGS,
edited by Samuel H. Yalkowsky

- Volume 13. ORPHAN DRUGS, *edited by Fred E. Karch*
- Volume 14. NOVEL DRUG DELIVERY SYSTEMS: FUNDAMENTALS, DEVELOPMENTAL CONCEPTS, BIOMEDICAL ASSESSMENTS, *edited by Yie W. Chien*
- Volume 15. PHARMACOKINETICS, Second Edition, Revised and Expanded, *Milo Gibaldi and Donald Perrier*
- Volume 16. GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICALS: A PLAN FOR TOTAL QUALITY CONTROL, Second Edition, Revised and Expanded, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*
- Volume 17. FORMULATION OF VETERINARY DOSAGE FORMS, *edited by Jack Blodinger*
- Volume 18. DERMATOLOGICAL FORMULATIONS: PERCUTANEOUS ABSORPTION, *Brian W. Barry*
- Volume 19. THE CLINICAL RESEARCH PROCESS IN THE PHARMACEUTICAL INDUSTRY, *edited by Gary M. Matoren*
- Volume 20. MICROENCAPSULATION AND RELATED DRUG PROCESSES, *Patrick B. Deasy*
- Volume 21. DRUGS AND NUTRIENTS: THE INTERACTIVE EFFECTS, *edited by Daphne A. Roe and T. Colin Campbell*
- Volume 22. BIOTECHNOLOGY OF INDUSTRIAL ANTIBIOTICS, *Erick J. Vandamme*
- Volume 23. PHARMACEUTICAL PROCESS VALIDATION, *edited by Bernard T. Loftus and Robert A. Nash*
- Volume 24. ANTICANCER AND INTERFERON AGENTS: SYNTHESIS AND PROPERTIES, *edited by Raphael M. Ottenbrite and George B. Butler*
- Volume 25. PHARMACEUTICAL STATISTICS: PRACTICAL AND CLINICAL APPLICATIONS, *Sanford Bolton*
- Volume 26. DRUG DYNAMICS FOR ANALYTICAL, CLINICAL, AND BIOLOGICAL CHEMISTS, *Benjamin J. Gudzinowicz, Burrows T. Younkin, Jr., and Michael J. Gudzinowicz*

- Volume 27. MODERN ANALYSIS OF ANTIBIOTICS, *edited by Adorjan Aszalos*
- Volume 28. SOLUBILITY AND RELATED PROPERTIES, *Kenneth C. James*
- Volume 29. CONTROLLED DRUG DELIVERY: FUNDAMENTALS AND APPLICATIONS, Second Edition, Revised and Expanded, *edited by Joseph R. Robinson and Vincent H. L. Lee*
- Volume 30. NEW DRUG APPROVAL PROCESS: CLINICAL AND REGULATORY MANAGEMENT, *edited by Richard A. Guarino*
- Volume 31. TRANSDERMAL CONTROLLED SYSTEMIC MEDICATIONS, *edited by Yie W. Chien*
- Volume 32. DRUG DELIVERY DEVICES: FUNDAMENTALS AND APPLICATIONS, *edited by Praveen Tyle*
- Volume 33. PHARMACOKINETICS: REGULATORY · INDUSTRIAL · ACADEMIC PERSPECTIVES, *edited by Peter G. Welling and Francis L. S. Tse*
- Volume 34. CLINICAL DRUG TRIALS AND TRIBULATIONS, *edited by Allen E. Cato*
- Volume 35. TRANSDERMAL DRUG DELIVERY: DEVELOPMENTAL ISSUES AND RESEARCH INITIATIVES, *edited by Jonathan Hadgraft and Richard H. Guy*
- Volume 36. AQUEOUS POLYMERIC COATINGS FOR PHARMACEUTICAL DOSAGE FORMS, *edited by James W. McGinity*

Additional Volumes in Preparation

Preface

Pharmaceutical knowledge has grown exponentially over the last 25 years. We now have a much clearer understanding of how drugs are absorbed into, distributed within, and cleared from the body. The potency of the agents with which we deal continues to increase, and our ability to unravel mechanisms of action proceeds. New drug entities—in particular peptides, proteins, and other biological response modifiers—are being developed and new challenges await the pharmaceutical scientist. Controlled drug delivery represents a field that must keep pace with the changing nature of chemotherapy. Tighter control of drug input into the body in both quantitative and temporal senses is crucial, and the fabrication of delivery systems must respond to this demand for increased sophistication.

Transdermal delivery has become an important means of drug administration. The number of investigators in this area has undergone a dramatic expansion and multiple symposia have focused on the subject. In this flurry of activity, developmental projects were established with little recognition of the inherent problems associated with chemical transport across the skin. As a result, several of these fledgling investigations have foundered. It is our belief that many of the problems encountered could (and should) have been foreseen. In some cases, the difficulties may not have been solvable; in others, we suspect, solutions were available but escaped attention because the problem was incompletely understood.

The first objective of this book is to highlight those key issues to which attention must be paid during the *early* stages of transdermal delivery system development. The subsequent aim is to indicate areas in which important progress is occurring and further basic research is needed. The contributors to this text have been

directed to emphasize the problems involved in percutaneous drug delivery and to describe rational approaches to circumvent such hurdles. Our authors were selected for their depth of knowledge and reputation in their subject areas, and for their ability to address objectively, without false optimism or uninformed pessimism, the topics of this book. We believe that they have performed this task effectively, producing a text that will facilitate and optimize future developmental programs in transdermal drug delivery.

Jonathan Hadgraft
Richard H. Guy

Contributors

Richard W. Baker Pharmetrix Corporation, Menlo Park, California

Ronald R. Burnette School of Pharmacy, University of Wisconsin,
Madison, Wisconsin

Saeho Chong Department of Pharmaceutics, State University of
New York at Buffalo, Buffalo, New York

Stephen P. Denyer Department of Pharmaceutical Sciences,
University of Nottingham, Nottingham, England

Donald T. Downing Dermatology Research Laboratories, Department
of Dermatology, University of Iowa College of Medicine, Iowa City,
Iowa

Nicholas Evans Department of Neonatal Medicine and Surgery,
City Hospital, Nottingham, England

Ho-Leung Fung Department of Pharmaceutics, State University of
New York at Buffalo, Buffalo, New York

Christopher L. Gummer Richardson-Vicks Europe, Rusham Park,
Egham, Surrey, England

Richard H. Guy Departments of Pharmacy and Pharmaceutical
Chemistry, University of California at San Francisco, San Francisco,
California

Jonathan Hadgraft Welsh School of Pharmacy, University of Wales
Institute of Science and Technology, Cardiff, Wales

Jorge Heller Polymer Sciences Department, S.R.I. International,
Menlo Park, California

Clare McNabb Department of Pharmaceutical Sciences, University
of Nottingham, Nottingham, England

Russell O. Potts Pfizer Central Research, Groton, Connecticut

Nicholas Rutter Department of Child Health, Queen's Medical
Centre, University of Nottingham, Nottingham, England

Richard J. Schmidt Welsh School of Pharmacy, University of Wales
Institute of Science and Technology, and Department of Medicine,
University of Wales College of Medicine, Cardiff, Wales

Ulrich Tauber Schering, Berlin, Federal Republic of Germany

Kenneth A. Walters* Eastman Pharmaceuticals, Rochester, New
York

Philip W. Wertz Dermatology Research Laboratories, Department of
Dermatology, University of Iowa College of Medicine, Iowa City,
Iowa

*Current affiliation: Pharmaserue Ltd., Loughborough, Scotland.

Transdermal Drug Delivery

Contents

<i>Preface</i>	iii
<i>Contributors</i>	ix
 1. Stratum Corneum: Biological and Biochemical Considerations	 1
<i>Philip W. Wertz and Donald T. Downing</i>	
I. Introduction	1
II. Production of stratum corneum	2
III. Components of the stratum corneum	7
IV. Barrier function of the stratum corneum	12
V. Perturbations of the stratum corneum	15
References	17
 2. Physical Characterization of the Stratum Corneum: The Relationship of Mechanical and Barrier Properties to Lipid and Protein Structure	 23
<i>Russell O. Potts</i>	
I. Introduction	23
II. Thermal studies of stratum corneum	24
III. Infrared spectroscopy studies of the stratum corneum	41
IV. X-ray diffraction studies of the stratum corneum	47
V. Conclusion	53
References	54

3.	Selection of Drug Candidates for Transdermal Drug Delivery	59
	<i>Richard H. Guy and Jonathan Hadgraft</i>	
	I. Introduction	59
	II. Biological properties of the drug	59
	III. Physicochemical properties of the drug	62
	IV. Determination of drug candidate feasibility	67
	V. In vitro assessment of skin permeability	75
	VI. System design	76
	References	77
4.	Cutaneous Side Effects in Transdermal Drug Delivery: Avoidance Strategies	83
	<i>Richard J. Schmidt</i>	
	I. Introduction	83
	II. Toxicological responses of the skin	84
	III. Conclusions	93
	References	94
5.	Drug Metabolism in the Skin: Advantages and Disadvantages	99
	<i>Ulrich Tauber</i>	
	I. Introduction	99
	II. The role of skin metabolism in systemic drug therapy	101
	III. The role of skin biotransformation in topical and transcutaneous drug therapy	104
	IV. Conclusions	110
	References	110
6.	Microbial Metabolism of Topically Applied Drugs	113
	<i>Stephen P. Denyer and Clare McNabb</i>	
	I. Introduction	113
	II. Microbiology of the skin	113
	III. Drug metabolism by skin microorganisms	122
	IV. Conclusions	131
	References	131

7.	Transdermal Drug Delivery Systems: Pharmacokinetics, Clinical Efficacy, and Tolerance Development	135
	<i>Sae-ho Chong and Ho-Leung Fung</i>	
	I. Introduction	135
	II. Relationships between in vitro and in vivo release rates from DDS	136
	III. Constancy in plasma drug concentration after transdermal DDS	137
	IV. Constancy in therapeutic effects after transdermal DDS application	139
	V. Pharmacological consequences of abrupt removal of transdermal DDS	145
	VI. Pharmacologic properties ideal for transdermal delivery	147
	References	148
8.	Transdermal Drug Delivery to the Newborn Infant	155
	<i>Nicholas Evans and Nicholas Rutter</i>	
	I. Introduction	155
	II. Mode of drug administration	157
	III. Structure of the newborn infant's skin	158
	IV. Skin permeability in the newborn	161
	V. Hazards of a high skin permeability	164
	VI. Transdermal delivery of theophylline	165
	VII. Transdermal delivery of other drugs	173
	References	174
9.	The In Vitro Evaluation of Transdermal Delivery	177
	<i>Christopher L. Gummer</i>	
	I. Introduction	177
	II. Delivery of the molecule to the skin surface	180
	III. Passage of the molecule through the skin	183
	IV. Recovery of the molecule in vitro	187
	V. Conclusions	193
	References	194

10.	Penetration Enhancers and Their Use in Transdermal Therapeutic Systems	197
	<i>Kenneth A. Walters</i>	
	I. Introduction	197
	II. Skin permeability	198
	III. Chemicals used to enhance skin permeability	203
	IV. Incorporation of enhancers into transdermal systems	229
	V. Conclusions	231
	References	233
11.	Iontophoresis	247
	<i>Ronald R. Burnette</i>	
	I. Introduction	247
	II. Overview	249
	III. Skin permselectivity	252
	IV. Ion transport via "pores"	260
	V. Modeling of iontophoretic transport	265
	VI. Conclusions	288
	References	288
12.	Materials Selection for Transdermal Delivery Systems	293
	<i>Richard W. Baker and Jorge Heller</i>	
	I. Background	293
	II. Device components	295
	III. Selection of membrane and matrix materials	298
	IV. Other components	305
	References	309
	<i>Index</i>	313

1

Stratum Corneum: Biological and Biochemical Considerations

PHILIP W. WERTZ and DONALD T. DOWNING *University of Iowa College of Medicine, Iowa City, Iowa*

I. INTRODUCTION

"Indeed, the *raison d'être* of the epidermis is to make the stratum corneum; this is its specific biologic mission." (1)

In order to fully understand the form and function of the stratum corneum it is helpful to know the processes involved in its formation from the living cells of the epidermis. Traditionally, several layers of living cells, constituting the Malpighian region, have been named either for their location or their appearance: the strata basale, spinosum, and granulare. The dead cells of the stratum corneum form the stratum lucidum (or compactum) and the stratum disjunctum. Although these terms or their English equivalents are still used, it is important to realize that the entire architecture of the epidermis constitutes a dynamic system in which each cell changes continuously during its passage from the basal layer where it is formed to the surface of the horny layer where it is discarded.

Study of the epidermis includes the morphology of the changing cell types, the dynamics of the differentiation process, the arrangement and chemical composition of the subcellular structures, the metabolic processes occurring in epidermal cells, and the location, composition, and physical properties of the epidermal barrier. All of these are discussed in this chapter as a basis for evaluating the physical and pharmacological aspects of transdermal drug delivery.